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ISSUE BRIEF

FDA Regulatory Process Has Become an Obstacle to Monoclonal Antibody Treatments for COVID-19

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Introduction

In the early stages of the pandemic, monoclonal antibodies (mAbs) provided benefits to vulnerable populations and six different mAbs were authorized to treat COVID-19.[1] These treatments work by mimicking the body's natural antibodies, which is why they are so valuable to the immunocompromised. No immune response is required.

However, the Food and Drug Administration (FDA) has pulled the authorization for all current treatments as the virus' continued mutations have undermined the effectiveness of the current mAbs. As of January 2024, the predominant COVID-19 strain is the JN.1 variant, which showed numerous mutations all at once. Tracing this evolution, Johns Hopkins University's Bloomberg School of Public Health notes that,

> A SARS-CoV-2 variant called BA.2.86 emerged a few months ago and caught virologists' attention because it contains many more mutations—about 30 of them—to evade immunity than any other variant circulating at that time. However, the BA.2.86 variant never came to dominate among the group of SARS-CoV-2 variants that were circulating in the late summer/early fall of 2023. The JN.1 variant is a descendant of BA.2.86 that has acquired the ability to transmit efficiently through an additional one or two mutations. It has the immune evasion of its parent but has now mutated to transmit more efficiently.[2]

How rapid? "In early November 2023, the JN.1 variant caused less than 5% of COVID-19 cases in the U.S. Now it is estimated to cause more than 60% of them".[3] Staying ahead of such rapid mutations is essential for minimizing future COVID-19 infections, hospitalizations, and mortality. The rapid growth of the JN.1 variant exemplifies how quickly the virus can mutate and emphasizes the need for a regulatory approval process capable of responding to a virus that constantly evolves.

A consistently changing virus that degrades protection from the current predominant treatments is a common problem. For instance, the constant mutations of the COVID-19 virus are why we need annual vaccine boosters. The same is true for the flu vaccine because the predominant flu strain varies from year to year. Consequently, an annual flu vaccine is required to ensure that individuals have the right antibodies.

The relevant question, consequently, is not whether mAbs are effective or ineffective. Their past success demonstrates that they can be effective, but only if cutting-edge mAbs stay one step ahead of the COVID-19 virus' mutations. It is important to note that past success at developing an efficacious mAb does not guarantee that future treatments will be successful. Undoubtedly developing efficacious mAb treatments tailored to the current COVID-19 strains is a huge scientific challenge. But it should be these scientific constraints, not regulatory inefficiencies, that dictate whether patients have access to mAb treatments.

The Potential mAbs Benefit

As noted by the Director of FDA's Center for Biologics Evaluation and Research (CBER), "vaccination remains critical to public health and continued protection against serious consequences of COVID-19, including hospitalization and death."[4] But what if you cannot take the vaccine?

Approximately 3 percent of U.S. adults, or around 8 million people, are immunocompromised.[5] Some are immunocompromised due to medical conditions like metabolic diseases including diabetes, chronic kidney disease, or HIV infections. Others are recipients of organ transplants, fighting diseases such as cancer, or are at risk of being severely immunocompromised due to the lifesaving medicines they must take. People who are immunocompromised are

disproportionately impacted by infectious diseases such as COVID-19 or the flu. They are at higher risk of experiencing more serious illnesses and at higher risk of dying. As the Centers for Disease Control and Prevention (CDC) explains,

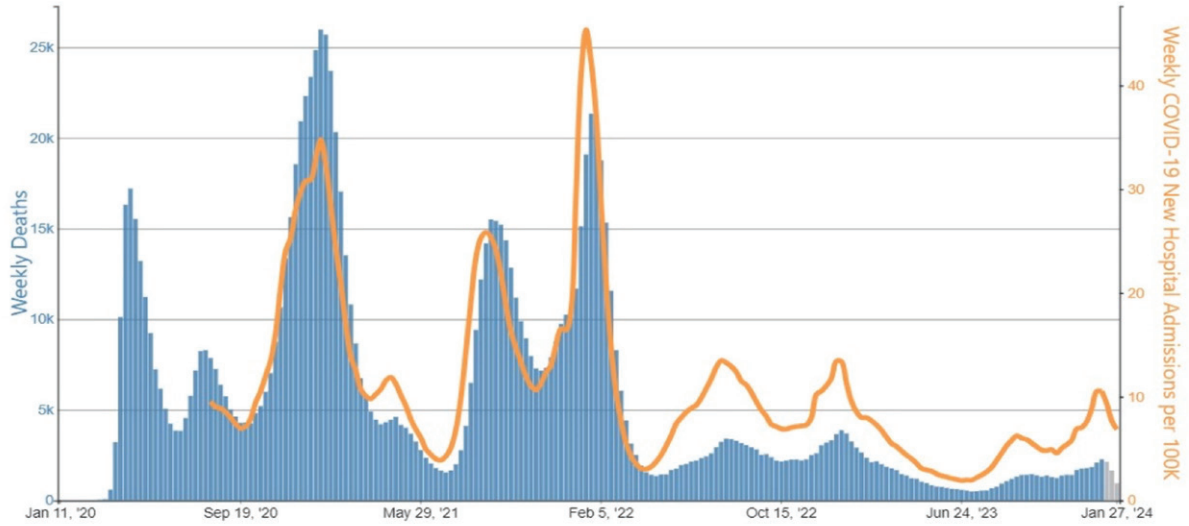
> People who are immunocompromised are a heterogeneous population, and the severity of COVID-19 can vary significantly in this group. Some individuals who are immunocompromised may have a higher risk of hospitalization, complications, or death, and some may have outcomes that are comparable to those in the general population.[6]

They also receive less protections from standard vaccines. For instance, a 2021 JAMA study examined the immune response to the COVID-19 mRNA vaccine in immunocompromised transplant patients. Although the authors found that the vaccine elicited some response, the "data suggest that a substantial proportion of transplant recipients likely remain at risk for COVID-19 after 2 doses of mRNA vaccine."[7]

Due to these risks, immunocompromised patients stand to benefit greatly if efficacious mAbs can be developed and approved. Given these realities, the regulatory environment should promote a wider array of treatment options, including the continued development of potentially efficacious mAbs. Unfortunately, in the fight against the mutating COVID-19 virus, we not only continue to lose important options, but the current regulatory structure erects barriers that reduce the potential to develop timely mAb therapies.

The timely development of therapies that are efficacious against the latest virus strains are essential given the continued surge in hospitalizations and deaths during the winter months. This impact can be visualized in Figure 1.

Figure 1. Provisional COVID-19 Deaths and New Hospital Admissions per 100,000 Population through January 27, 2024



Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2024, February 05. https://covid.cdc.gov/covid-data-tracker

Figure 1 presents the weekly deaths (blue bars, left-hand scale) and hospitalizations per 100,000 people (orange line, right-hand scale) from January 2020 through January 2024. While the surge during the months of December and January during the current winter season was much smaller than previous years, a clear seasonal pattern remains. This surging pattern coupled with the tendency for the virus to mutate creates significant health risks for people, particularly the immunocompromised, during the winter cold and flu season – now more accurately described as the cold, flu, and Covid season.

Efficacious treatments and vaccines help minimize the severity of the annual seasonal surges. Alternatively, should treatments not be efficacious against the rising dominant strain for a future seasonal surge, the hospitalization and mortality rates could peak at significantly higher levels. Minimizing the regulatory delays for approving efficacious and safe mAbs that target the expected seasonal COVID-19 strains will improve the health system's ability to minimize the severity of the now expected seasonal Covid surges, particularly for immunocompromised patients.

Overburdensome FDA Regulation Inhibiting mAb Development

The FDA offers a pathway to adjust current vaccines to be efficacious against the expected strain of viruses such as influenza and COVID-19. These updates are necessary because these viruses consistently mutate – sometimes minor mutations, other times major mutations. With respect to the seasonal influenza, the FDA has been implementing an annual review and update process that attempts to ensure the greatest possible efficacy against the expected influenza strain.

Weir and Gruber (2016) provide an overview of the annual review and update process that "is a complex, lengthy process that requires extensive collaboration among influenza manufacturers, vaccine regulators, and global public health laboratories. The process begins with the recommendations, coordinated globally by the World Health Organization (WHO), for the virus strains to be included in the vaccine."[8]

After the WHO provides the relevant recommendations that are available each February, "the FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC), typically in late February or early March, to recommend the virus strains that should be included in FDA-licensed influenza vaccines for the next winter influenza season in the United States."[9] To gain regulatory approval in the U.S. for the updated influenza vaccine,

> licensed influenza vaccine manufacturers must submit a supplement to their license for review and obtain FDA approval before the updated version of the influenza vaccine containing new virus antigens can be distributed. Such supplements to inactivated and recombinant protein seasonal influenza vaccines do not require additional clinical data specific for the new strain. Supplements to the licensed live influenza virus vaccine require a study in approximately 300 adults prior to approval of the new strain to verify adequate attenuation. Manufacturing of influenza vaccine takes place over an approximately 6-month time frame beginning prior to the VRBPAC strain selection and lasting until mid-summer, when the trivalent or quadrivalent vaccine is formulated, filled, and distributed.[10]

The FDA – and specifically CBER -- has adopted this model as applied to COVID-19 vaccines. Consider how CBER approaches the development of the updated COVID-19 vaccines,

> COVID-19 vaccine development may be accelerated based on knowledge gained from similar products manufactured with the same well-characterized platform technology, to the extent legally and scientifically permissible. **Similarly, with appropriate justification, some aspects of manufacture and control may be based on the vaccine platform, and in some instances, reduce the need for product specific data.** (emphasis added)[11]

With respect to the 2023-24 Winter season,

> FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on June 15, 2023, to discuss and make recommendations for SARS-CoV-2 strain(s) for updated COVID-19 vaccines for use in the United States beginning in the fall of 2023.

> For the 2023-2024 formulation of the COVID-19 vaccines for use in the U.S. beginning in the fall of 2023, the committee unanimously voted that the vaccine composition be updated to a monovalent COVID-19 vaccine with an XBB-lineage of the Omicron variant. Following discussion of the evidence, the committee expressed a preference for XBB.1.5.
>
> During this meeting, the advisory committee was informed of the manufacturing timelines, they reviewed the available data on the circulation of SARS-CoV-2 virus variants, current vaccine effectiveness, human immunogenicity data of current vaccines against recently circulating virus variants, the antigenic characterization of circulating virus variants, animal immunogenicity data generated by new candidate vaccines expressing or containing updated spike components, and preliminary human immunogenicity data generated by one XBB.1.5 candidate vaccine.
>
> Based on the totality of the evidence, FDA has advised manufacturers who will be updating their COVID-19 vaccines, that they should develop vaccines with a monovalent XBB 1.5 composition.[12]

There are many apparent similarities between the influenza and COVID-19 pathways including the cooperation between the government and manufacturers, the monitoring of the virus mutations, and finally a recommendation that reflects the best available data with the goal of ensuring that the updated vaccine is safe and efficacious against the expected virus mutation.

The process is far from perfect; there have been instances where the mutated influenza virus differs from expectations, for instance. Overall, the methodology provides an effective pathway that allows manufacturers to adjust their vaccines in response to ever-mutating viruses without imposing a regulatory approval process that would prevent the vaccines from being available to people in time for the seasonal infections.

The FDA achieves this by not requiring vaccine developers to conduct vaccine trials that simply duplicate the information already gained from past trials. The regulatory structure captures the knowledge learned creating past vaccines to lower the costs and time required to develop treatments that are tailored to the current variants. This structure creates greater regulatory certainty, lowers the cost of updating the treatment to be effective against current virus strains, and speeds up the development time.

Unlike vaccines, which are regulated by CBER (Center for Biologics Evaluate and Research), mAbs are regulated by CDER (Center for Drug Evaluation and Research). CDER has not developed the same pathways that would expedite the development of seasonal treatments that are tailored toward the expected mutated COVID-19 virus strain. Instead, mAbs came on the market as efficacious and safe treatments to the original COVID-19 strains. But, when natural virus mutations occurred, the platforms and learnings were not used as a starting point for developing adjusted mAbs that would be more efficacious against the current COVID-19 strain compared to the existing treatment. Instead, mAbs were taken off the market due to lack of efficacy with developers needing to restart the entire approval process for any mAb that targets the latest COVID-19 strain.

“When natural virus mutations occurred, the platforms and learnings were not used as a starting point for developing adjusted mAbs that would be more efficacious against the current COVID-19 strain compared to the existing treatment.

Taking the regulatory step of removing mAbs from the market implicitly assumes that efficacious mAbs should be able to generate longer range protections for patients that are robust against many different mutations to the original virus, and that rapid updates to these treatments that target the expected strain are not possible. These assumptions may be appropriate, but they could also be wrong.

The mAbs developed to date have not been capable of providing robust protection against the mutating COVID virus. Based on the vaccine experience, this expectation may be unrealistic. The relevant question consequently becomes can annual modifications to mAbs create improved protection against infection, hospitalization, and/or mortality that stays current against the mutating COVID-19 virus. CDER's current regulatory pathway for mAbs denies this potential by ensuring any mAb enhancement cannot be expeditiously approved. As a result, mAbs are not currently offered an opportunity to develop the efficacious modifications necessary to treat the latest mutations of the virus.

Reforms to Reduce Regulatory Obstacles

If a treatment is not efficacious against the strain that is prevalent when it is approved, then its value to patients is lost. The large risks that this will occur under the current regulatory structure make it exceedingly difficult, if not impossible, to develop innovative mAbs that keep pace with the mutating COVID-19 virus. For this reason, the FDA's current regulatory process – specifically within CDER – is discouraging the development of potentially valuable treatment options.

To minimize the regulatory burdens, the FDA should adopt a consistent regulatory structure that accounts for COVID's dynamic disease environment and minimizes the government-created burdens that can inhibit the development of potentially efficacious COVID-19 treatment options. As described above, this regulatory pathway already exists. The vaccine regulatory framework used by CBER can serve as a model to help CDER expedite the production of any mAb that proves to be efficacious against the latest variant.

> "Lessening these regulatory burdens could reduce important obstacles that are inhibiting their development, particularly the excessive amount of time that is required to follow the current regulatory pathway.

Applying the vaccine approach to the development of mAbs would leverage the research platforms and require less product specific data (where appropriate). Lessening these regulatory burdens could reduce important obstacles that are inhibiting their development, particularly the excessive amount of time that is required to follow the current regulatory pathway. The excessive time it currently takes to develop a mAb for the current strain raises the risk that a different mutation will be the dominant one by the time an innovative mAb can finally become available to patients.

Appropriately applying the platform approach that the CBER uses for vaccines to the mAb technology would remove a burden discouraging manufacturers from developing mAbs tailored to the latest variants. The result could improve health outcomes for vulnerable patient groups and help us stay one step ahead of the consistently mutating COVID-19 virus.

Conclusion

Effective treatments for COVID-19 must account for the virus' mutations. The current regulatory pathway for vaccines via CBER accounts for this reality by creating a pathway that enables the expeditious development and approval of vaccines that are efficacious against the expected variant during the winter months – the months when infections, hospitalizations, and mortality spike. This pathway does not currently exist for mAbs, which are managed by CDER.

Unsurprisingly, there are no longer any mAbs that are efficacious against the current COVID-19 strains available to patients. This deficiency imposes a higher cost on immunocompromised patients who benefit less from the vaccines and face greater health risks from the COVID-19 virus. Properly applying the vaccine approval pathway to mAb treatments would better enable the availability of treatments that prove efficacious against the latest COVID-19 strains in a timely fashion.

mAbs and vaccines both face the same limitations against the mutating COVID-19 virus. Consequently, they both require a flexible regulatory environment that can enable an efficient approval process that enables manufacturers to produce vaccines and mAbs that are appropriate for the virus' current mutations. This process exists for vaccines but does not for mAbs. Creating an appropriate and collaborative review and approval pathway for mAbs at CDER could address this problem and significantly improve health outcomes for our most vulnerable: immunocompromised patients, now and into the future.

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Endnotes

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About the Author

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Wayne H. Winegarden, Ph.D. is a Senior Fellow in Business and Economics at the Pacific Research Institute and director of PRI's Center for Medical Economics and Innovation. He is also the Principal of Capitol Economic Advisors.

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